UNOFFICIAL TRANSCRIPT[1]
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
March 16, 2005
Radisson Hotel SeaTac
9:00am – 2:30pm

Committee Attendance:
Carol Cordy (Acting Chair)
Robert Bray, M.D.
T. Vyn Reese, M.D.
Angelo Ballasiotes, Pharm.D.
Jason Iltz, Pharm.D.
Janet Kelly, Pharm.D.
Patti Varley, ARNP

A quorum was shown for all Pharmacy & Therapeutics Committee motions, 2nd's, and votes.

9:00 a.m. - Committee came to order.

WELCOME & INTRODUCTIONS

Carol Cordy: I'd like to welcome you all here today. And let's start out by introducing everyone. Go ahead.

Kristi Coulter: Kristi Coulter, L&I.

Jaymie Mai: Jaymie Mai, L&I.

Janet Kelly: Janet Kelly, member of the P&T.

T. Vyn Reese: T. Vyn Reese, internal medicine, Geriatrics Seattle, member of the committee.

Angelo Ballasiotes: Angelo Ballasiotes, member of the committee and Central Washington Conference in Mental Health in Yakima.

Bob Bray: Bob Bray from Spokane Family Physicians, member of the committee.

Patti Varley: Patti Varley, child and adolescent Psych Nurse Practitioner, Children's Hospital, member of the committee.

Jason Iltz: Jason Iltz, member of the P&T.

Jeff Graham: Health Care Authority.

Andre Rossi: Andre Rossi from the Department of Corrections.

[1] For copies of the official audio taped record of this meeting, please contact Erika Clayton at (206)521-2027 pdp@hca.wa.gov.

Erika Clayton: Erika Clayton, Health Care Authority.

Duane Thurman: Duane Thurman, Health Care Authority.

Donna Marshall: Donna Marshall, Uniform Medical Plan.

Carol Cordy: I think we have Kim Peterson and Mark Helfand on the line and they'll be presenting the OHSU update on the drug class of Triptans. And after their presentation we'll have an opportunity for stakeholders to give their brief presentations. We'd like to limit those to 3 minutes if you can. Has anyone else signed if they wanted to present [unclear]?

Jeff Graham: Carol, we have a brief announcement that we'd like to make. Duane, would you like to make that announcement? As you have noted that we were going to review the atypical antipsychotic [unclear] deliberations and thinking about it we have decided to delay that in order to give us more time to do a better job of reviewing that class. That will be in October.

TRIPTANS
Update of Drug Class Review

Carol Cordy: So, Kim, are you on the line?

Kim Peterson: Yes.

Mark Helfand: I am, too. This is Mark.

Carol Cordy: Okay.

Mark Helfand: Did you want us to start?

Carol Cordy: Yes, why don't you go ahead.

Mark Helfand: On the Triptan?

Carol Cordy: Yes.

Mark Helfand: Do you have the slide show?

Carol Cordy: Yes. Can somebody dim the lights.

Mark Helfand: And you can hear me all right.

Carol Cordy: Great.

Mark Helfand: Yeah. Okay. Well, this is an update that was put out in September. If you- what we're trying to do today, since you've already looked at the Triptans at least once, I think twice, is try to highlight the new information so you can skip to I think the- skip through the first few slides until you get to the one that says Update #2: Methods. Okay, which just says no changes to this update to the Key Questions, Inclusion Criteria or Search Strategy. The next slide about the previous systematic reviews, this is old information, I'm going to skip that, too. The next slide, Efficacy: Head-to-Head Trials, there are two new head-to-head trials covered in this review and that's really the main new studies. Also in this review there- we included a met analysis pertaining to some of the studies used in encapsulated versions of the Trip tabs and I'll get to that later. The next slide shows which head-to-head studies- what the head-to-head studies that are included actually compared. You can see that- reading across there are five Eletriptan studies. And reading across and down you see what the other head-to-head studies included in the review. The first thing I'm going to do is discuss the Eletriptan studies, the ones highlighted in yellow with asterisks. Are they highlighted in yellow with asterisks?

Many: No.

Mark Helfand: Oh, well, we're reading across the Triptan studies and there should be numbers in the Nara, Suma and Zolmi columns. Are there? This is slide 9.

Carol Cordy: Yes.

Mark Helfand: Okay. So we're going to talk about those first. So, essentially, these were- these studies that compared Eletriptan to other Triptans, they were reasonably well done studies and in order to make a fair comparison the maker of Eletriptan wanted to have a double blind study. So they put the comparator, Sumatriptan in most of the studies, into a capsule. The studies tended to show that Eletriptan was more efficacious. But in the scientific literature a discussion emerged about whether the capsule itself, which is just a simple gelatin capsule, could effect the kinetics and make Sumatriptin appear less effective than it actually is. The evidence for that claim that the capsule causes problem is confusing. There is data on both sides. The maker of Eletriptan has done a lot of kinetic- nonclinical but kinetic studies trying to demonstrate that the kinetics aren't affected. In our previous report we excluded- we included these Eletriptan studies but we separated them off and we said we don't know what to make of this because we don't know if the results we're seeing are related to the method and the study design, the method of double blinding the capsules or to the drugs themselves. So while we don't think that they should be excluded, we separated them off. We made a commitment at that time to look more carefully at the issue. And at this time what we've done is include a meta-analysis of Triptan studies to try to examine whether we could determine whether encapsulation affected the

apparent effectiveness of Sumatriptan. This meta-analysis is in our report, but it isn't published in a [unclear] journal yet, and we hope and plan to do that.

The next slide says encapsulation meta-analysis (table 4, page 14), which is referring to the report. And it is probably better to look at that table while I'm talking about this. But looking at both the pain relief and the pain free responses of 2 hours, we had a paradoxical result. The result was after adjustment for age percent female, percent with severe versus moderate baseline pain, because all these studies patients either have moderate or severe baseline pain. But after adjustment for those factors, encapsulation was still associated with lower efficacy for Sumatriptan. But as I said, paradoxically, in studies of Eletriptan versus encapsulated comparators, the effect sizes were larger, that is the average effect of the Eletriptan was higher than it was in other studies of Eletriptan. Whereas Sumatriptan and other comparators were less effective than in other studies of them. We don't know how to explain these results. We don't think that they're related to the capsule because we really doubt that a capsule could have any effect to improve Eletriptan. So despite the fact that we've done this extra work, we don't have a clear answer on encapsulation. But our answer on the studies is this: The studies indicate- and because of these questions I should say we also looked at placebo controlled trials of Eletriptan to make indirect comparisons. And as you know from the previous meta-analysis, the ones we skipped in the slide earlier, those show Eletriptan to be at least as efficacious as others. And that's our conclusion, too, that we can say that it's as efficacious as others, but the evidence that it's more efficacious is still questionable because of these confusing results related to our analysis of these encapsulation studies. So it may well be better, but these studies are not reliable enough evidence because of those results to say for sure that it is. On the other hand we don't want people to throw out Eletriptan as if it had no studies of effectiveness. Our conclusion is that the body of evidence is that it is as efficacious as least.

The next slide just shows that- well, in this next slide we're going to now turn our attention to the studies of Rizatriptan versus Naratriptan and Sumatriptan. And those slides- if you go on to the next slide it says Riza versus Naratriptan. This is old information. I'm not going to repeat it. As well as the next slide; Riza versus Sumatriptan, which is also an older study that was included in our previous reviews. I do want to point out in this study about Riza versus Suma, or this slide, that 24 hours sustained relief and long-term consistency have not been evaluated in head-to-head trials of Rizatriptan. That's important because Rizatriptan seems to have superior results for 1 and 2 hour pain relief for essentially how fast it works. But the flip side of that is sustained relief. And while there's no strong reason to suspect Rizatriptan isn't as good in sustained relief, it's worth pointing out that there aren't head-to-head trials examining it.

The next slide is just what we want to talk about next are the Suma versus Nara and Suma versus Zolmi studies. And Suma versus Nara, the next slide,

it says 1 fair-quality trial with no difference in most effectiveness outcomes and better 4-hour pain relief from Sumatriptan. Suma versus Zolmi is also an older study that was included in our previous review. Next slide says Suma versus Zolmi. And as before, there isn't anything new to say about it is what I'm trying to say.

The limitations of the head-to-head trial, the next slide, most trials only report results from three or fewer attacks, although two compared Zolmi and Suma across 6 attacks. The proportion of patients that responded at 2 hours in 80-100% of attacks was found to be an unreliable measure of consistency. And what we're trying to say there is that we don't really have good evidence on the consistency of headache relief for a particular Triptan over time. Something that patients might be interested if they're using drugs month-to-month not just headache to headache over three episodes. And also head-to-head trials don't really say much about function, work productivity or quality of life, although that study of Riza versus Suma does report return to normal function within 24 hours. But work productivity, quality of life over time, over weeks and months, the studies really don't discuss that.

Next slide it says limitations of head-to-head trials. Almotriptan has been evaluated in 2 head-to-head trials, both of which are of poor quality and we have discussed this at length in previous reports. And also Frovatriptan, 6 studies were submitted to the FDA when Frovatriptan was approved. None of them have been published in journals and the information in the FDA material is not really complete enough to evaluate the studies so that we haven't completed them. Finally, Sumatriptan has been reformulated and I believe that more trials are planned for it. We reviewed a limited number of placebo controlled trials, but really can't make strong conclusions about the comparative efficacy of the newer formulation until more evidence is published or reported in full form.

Next slide it says Update #2 Efficacy: Placebo controlled trials. And as we said, they're looking primarily at placebo controlled trials. There's at least equivalent to cross efficacy measure for Eletriptan compared to conventional Sumatriptan, for Eletriptan and for Almotriptan. The reformulated Sumatriptan we found 1 placebo controlled trial suggesting at least equivalence to conventional Sumatriptan. And the percent of patients who were pain free at 2 hours. But as we say, we think more is coming out. The literature search for this version of the review ended last March. The report was put out last September and we're aware of a few trials that are being published or have been published since then which will be incorporated in the next report.

If you go on to the next slide it says Efficacy: Active-Controlled Trials. And we don't have anything new to say so I would skip that slide as well as the next one which says other controlled trials. There is a- it says use of Triptans

in mild migraine attacks. The next update, not this one, may include a new study of Frovatriptan for mild migraine attacks, but the studies that were published in time for this version have mixed results on how good they are. The main problem with studying Triptans for mild attacks is that a lot of them wouldn't have progressed. A lot of them, the placebo control group- the control group rates of relief are high. However, using them early in an attack is how many people advise patients to use Triptans. And it's how many patients do use Triptans. So there is a gap between what the studies and the literature have examined. So that is relief of moderate to severe, where you've waited for the headache to get bad enough to qualify versus what's done in real life, which is treat earlier.

And the next slide is also unchanged from before, that there is essentially insufficient evidence on the consistency of relief for attacks. Next slide says safety and subgroups nothing new. If you have the report I think I can tell you what page the summary table is on. But the main points from this update are to clarify something we don't think we were clear enough on before that the exclusion of the head-to-head trials of Almotriptan and previously Eletriptan don't mean that those drugs aren't effective. Of course they are. They were approved by the FDA because they were better than placebo. And all we can state is we can't find strong evidence that they're better. Okay?

Carol Cordy: Thank you.

Mark Helfand: Mm hm.

Carol Cordy: Are you going to stay on while we discuss and ask questions:

Mark Helfand: Yeah.

Carol Cordy: Why don't we open it up to the committee. Any questions or comments?

Vyn Reese: Mark, hi, this is Vyn Reese. And based on your current update it doesn't look like there's anything new in the Triptan group as far as any drug being superior to any of the others. Is that correct?

Mark Helfand: Well, there's nothing new. I think previously you had discussions about what the studies already included were saying about comparative effectiveness. But I would say that unless I'm wrong the two new included trials, maybe Kim, could you just tell them briefly what those trials were, which ones they were?

Kim Peterson: Yes. There was a trial of Eletriptan versus encapsulated Naratriptan and one trial of Eletriptan versus encapsulated Zolmitriptan.

Mark Helfand: Right. So those are discussed in the meta-analysis. And for the other comparisons nothing new.

Vyn Reese: Thank you.

Bob Bray: This is Bob Bray. I'm wondering about the studies about Frovatriptan. Were you guys able to examine those studies the [unclear] used? Or since they've not been published…

Mark Helfand: Yeah. I think I misspoke. I said 6. It's actually 5 studies that were submitted to the FDA and which are discussed, of course, on the product label for Frovatriptan. The studies were submitted to the FDA in the year 2001, which I think means it's unlikely they'll ever be published since it's already been 4 years since they were reported to the FDA. The FDA has summarized their interpretation of these studies in the product label. So you can get a pretty clear idea of what they said from there, but I'll just say a few words about them. They were comparable to may other placebo controlled head-to-head trials with Triptans in the basic design; that is you wait until you get a headache that's moderate to severe and then you take whichever Triptan you're assigned. Four of them were placebo controlled. One compared Frovatriptan to Sumatriptan. In the placebo controlled trials Frovatriptan was better than placebo for 2-hour pain relief. At least in the material we have from the FDA site, they didn't report pain free outcomes at all. According to the FDA, in the placebo controlled trials 2-hour pain relief rate or 38-46%, that's a range, for Frovatriptan versus 21-27% for placebo. And about half the patients, 50% of the subjects needed to take a 2nd Frovatriptan within 24 hours. In the only head-to-head trial Sumatriptan was significantly better than Frovatriptan. Sumatriptan was significantly better than Frovatriptan at 2 hours and at 4 hours. The 2 hour response rates were 47% for Sumatriptan and 37% for Frovatriptan. At 4 hours the percentages were 70% for Sumatriptans and 62% for Frovatriptans. This study, too, did not report pain free outcomes. There are 2 studies, there are many publications about Frovatriptan. I need to point that out. It's not like nothing has ever been published. What we're talking about is whether those trials have been published. Almost all the publications- we're aware somewhat about 40 publications about Frovatriptan, but most of them are reviews or have other problems that aren't really trials at all, those kinds of things.

There are some more recent studies of Frovatriptan that may warrant inclusion in our next review. One of them is a study of treating a migraine when it's still mild, and another by an author named Filberstein was published in 2004, which is the first of 2 recent studies of Frovatriptan in women with menstrual migraine, where they actually don't wait to get a headache, they take it in perimenstrual time and avoid headaches by it. And at present- it's a form of prophylaxis although many of these patients predictably will have migraines with every period, so it isn't really a prophylaxis in the sense of we usually

think about it. Because there's such a high probability that they would get a migraine headache if they didn't take something. So we may add that question and those two studies if they're both published, one is published already, in the next version of the review. But that's what we really know about the Frovatriptan studies.

Carol Cordy: Thank you. Any other questions or comments? I have a question. This is Carol Cordy. And this is maybe wordsmithing, but it seems like with all these reports we use efficacy and effectiveness and efficacious and effective somewhat interchangeable. And I noticed on the report on the inhaled corticosteroids that we'll get to later that they very clearly distinguish between effectiveness and efficacy. Are these studies would you say efficacy studies or effectiveness studies?

Mark Helfand: These are efficacy studies. These are studies that were done primarily for regulatory approval. They don't attempt to show the generalizability or the applicability of the results in general practice. In fact, the terms of the studies requiring people to have a severe or moderate headache before they take a pill are quite unlike how people use medication in everyday life. And, more importantly, they're short term. They usually allow only three headaches. You know, I think an effectiveness study in the area of Triptans could look at work productivity, quality of life over many many months and a year. Now there are studies like that, especially early studies of injectable Sumatriptan where a very nice amount of effectiveness literature was generated showing that Triptans seemed to make a difference in people's lives, but they're not comparative. So the report does have a summary of those uncontrolled effectiveness studies. What we're lacking are controlled effectiveness studies or comparative ones to say whether one's better than another. And a lot of different drug classes, if some drugs in the class have been evaluated more thoroughly, that is certain outcomes have been looked at that haven't been looked at for others, for example, in the statins, some of them have been examined and studied that measure cardiovascular mortality, others haven't. People are interested in knowing that, even though it's not really comparative information saying whether one's better than another. In this class there's a lot of information about what outcomes are important to patients. There's a lot of head-to-head trials, but it's mostly efficacy evidence.

Stakeholder Input

Carol Cordy: Thank you. If there aren't anymore comments or questions from the committee, we'd like to open it up to stakeholders. I don't have a timer. Does somebody want to take that on? So if we- we'd appreciate it if you'd limit your comments to 3 minutes. And I think whoever is keeping track of the time can maybe raise your hand when there's 16 seconds left and we can maybe wrap up. We appreciate your comment. I have seven people who signed up who wanted to speak on the Triptan. And we'll start with Jennifer-

not sure how you pronounce your name. Maybe you can pronounce your last name for me. And if you would let us know if you're speaking for yourself or if you are representing someone else or a company.

Jennifer Birzana: Jennifer Brezzana. Members of the committee, good morning and I thank you for the opportunity to share with you the importance of continuing Imitrex's status on Washington Medicaid's Preferred Drug list. My name is Jennifer Brezzana. I'm with GlaxoSmithKlein Medical Affairs. Imitrex is the most widely studied Triptan on the market and therefore has a vast library of [unclear] efficacy data. This experience has made Imitrex the gold standard as well as the market leader. Imitrex is the only Triptan available in 3 formulations, and it's flexibility allows patients to use the Imitrex injection as well as the tablet in the same 24-hour period. This treatment strategy is unique to Imitrex because you know that using 2 different Triptans in the same 24-hour period. For instance, Imitrex injection and a different Triptan is actually contraindicated. We know a single migraine patient can have several different presentations of their migraine, and 30-40% of the time nausea and vomiting interferes with the absorption of oral and melt tablet formulation. Therefore, flexibility en route of administration is necessary. Speed of onset is one of the top 3 most important considerations among migraine patients. Onset of headache relief begins as early as 10 minutes with Imitrex injection and 15 minutes with the nasal spray. In January of 2004, Imitrex tablets were redesigned to disintegrate rapidly, regardless of the presence of gastric status, which we know occurs as part of the migraine process. Reformulated Imitrex 100 mg tablets now have an onset of 20 minutes for the first and only oral Triptan that has surpassed the 30 minute onset point.

Getting pain free is also one of those top 3 most important treatment considerations for migraine patients. Published data with reformulated Imitrex 100 mg tablets has pain free rates at 75% at 2 hours. So 3 out of every 4 patients are pain free at 2 hours. When comparing among the Triptans, I'd like the committee to remember a few things; no Triptan has proven superiority to Imitrex in adequately designed and well controlled study. Several trials that have been mentioned that have compared Imitrex to Well Pax using over encapsulated Imitrex. Your report illustrates the decrease in efficacy that occurs as a result of over encapsulation and excluded trials of poor design from its analysis. The OHSU Triptan report however, does use the Ferrari meta-analysis and discusses some of the conclusions. The Ferrari meta-analysis did include over encapsulated Imitrex data. When comparing Imitrex to Maxalt the OHSU Triptan report draws it's conclusion from one of at least 5 head-to-head trials. The findings of the single trial are not consistent among the other head-to-head trials. No Triptan is compared itself to the reformulated Imitrex and, as was mentioned, no data using reformulated Imitrex was included in the OHSU Triptan report. It is important to remember Imitrex has minimal drug interactions. It is metabolized by the

monoimmunoxidaze system, not the cytochrome P450 system, therefore it avoids further complication of the clinical [unclear] making process.

In closing, the clinical experience and multiple formulations of Imitrex offer you flexibility to utilize a stratified [unclear] with proven efficacy and safety.

Carol Cordy: Thank you. Dr. Stewart Tepper.

Stewart Tepper: Hi. GlaxoSmith-Kline asked me to come talk a little bit about my clinical experiences with Triptans in terms of patient care, and I think that's what I really want to do rather than the "my Triptan is better than your Triptan, nah nah nah" thing. I really want to talk about what we're trying to do with patient care. And what we're trying to do is follow our guidelines of our professional organizations which is the US Headache Consortiums set guidelines for the ACP and the AAFP and the AAN several years ago. And the most important outcome measure that they set was pain free 2 hours, preferably without recurrence, and we actually did a study looking at 27 different items of patient outcome, and that's what we came up with; pain free, 2 hours. And that's linked to not having recurrence. So that's what we're really after.

Now clinically what happens is you get into this bind where what we're talking about is Triptan A, Triptan B, Triptan C, all in the oral form. But in fact it's the very ability of the attacks that can leave the patient to get stuck and not be able to function. And we're trying to reduce disability and impact and timeloss with the patients in addition to achieving that. So the sticky wicket is that the FDA forbids us to switch the Triptans within the same day. So what you can do is you can use a tablet if the attack occurs during the day, but if the attack occurs full blown in the morning or has a quick onset to nausea and vomiting or the tablet fails and the patient is stuck, then the patient can't rescue with an injection if they use any of the other Triptans except Sumatriptan. So what ends up happening is that the flexibility of form of Sumatriptan leads to- allows you to treat the variability of the attack. And that's the clinically significant aspect. That's why I use Sumatriptan first, because it gives me that flexibility for the patient. Now this reformulated Sumatriptan that the Oregon people talked about is a new rapid release technology that gets the tablet in and absorbs faster. And all of the fast acting Triptans have a statistical onset of effect in the treatment of moderate to severe pain in about 30 minutes. The new formulated Sumatriptan in the 2 large placebo controlled trial, one of which has been accepted for publication next month, had the statistical onset of effect at 20 minutes. And so it does look like the RT technology allows for a faster onset and higher pain free numbers at 2 hours. So you're aiming at the pain free numbers. It looks like the tablet- the new tablet provides optimal aspects of that and the injection is your back up. And then you also have nasal spray, which can be used when nausea is too great.

So summarize, I'm aiming to fit the Triptan to the clinical situation. And I use Sumatriptan because of 1) the unique technology of the new pill, 2) the backup of the injectable which allows the patient to treat and prevent the need for the expensive trips to the emergency room and disruptive trips for urgent care backup. Thanks.

Carol Cordy: Thanks. Larry Martinez?

Larry Martinez: Good Morning. My name is Larry Martinez. I'm a clinical education consultant for Pfizer Incorporated. I would like to present a statement on behalf of Pfizer regarding the Triptan review conducted by the EPC. On page 12 of the review it is indicated that a meta-analysis of the Triptan data was conducted to examine the effects of encapsulation on pain relief and pain free response at 2 hours. We would like to point out that this meta-analysis was conducted in spite of a previously published meta-analysis by Ferrari, et. al., that appeared in the journal Lancet. We would request the committee defer consideration of the EPC meta-analysis until A) significant detail concerning the methodology used to conduct the meta-analysis has been provided. At this point we've only received a summary of the methods. In addition, differences in capital manufacturing by different companies should be addressed. Encapsulation specifically is a methodology widely used in the industry. In fact, many of the competitors in this market used encapsulated comparator agents during clinical studies. Encapsulation is a technique approved by the FDA and often the only option for preserving scientific integrity in cases, for example, when competing agents refuse to supply a blinded drug.

Continuing, we request a discussion of the bioequivalence studies that has been conducted when encapsulation is utilized. If a contention that encapsulation is a major issue is presented, and that encapsulation ultimately impacts efficacy in this class of drugs, then significant time ought to be devoted to address the bioequivalence and formito-kinetic data that has been conducted through and FDA mandate aimed to ensure that encapsulation did not impact these very parameters. While access to this data is readily available, none of these studies were discussed in the EPC report. At the time of the report, the Ferrari meta-analysis had been published in Lancet and thus was peer reviewed and thus put through a peer scrutiny. We would ask that the EPC meta-analysis be published and go through the same level of scientific scrutiny prior to being taken into consideration. To date none of these steps have been taken.

Finally, it is Pfizer's contention that if data for all of the published Sumatriptan efficacy trials be compared to Sumatriptan performance data derived from studies with Eletriptan utilizing encapsulation. Encapsulated Sumatriptan outperformed nonencapsulated Sumatriptan in most studies.

Thus, Sumatriptan, or encapsulation rather, did not diminish Sumatriptan's efficacy.

Published data supports the premise that Sumatriptan is an inferior drug to Eletriptan in 2-hour headache response and in pain relief to 2 hours; parameters that are recognized by the FDA to be important outcome parameters for this class…

Carol Cordy: Okay. Can you wrap up time?

Larry Martinez: Finally, we ask that you take into consideration that if encapsulation was such a contentious issue, then why would the FDA approve this agent and allow the data on efficacy to appear in the package labeling.

Carol Cordy: Thank you.

Larry Martinez: Thank you.

Carol Cordy: Steve Singer. Dr. Steve Singer?

Steve Singer: My name is Robert Steven Singer. I am a neurologist and a headache specialist for the past 20 years, editor of the King County Medical Society Journal. I have seen 75,000 headache patients and probably 25,000 since we've had the Triptans around. We know that about 30 million people in America suffer migraine. There's some days in my office when I'm convinced when half of them have called us, by the way. Stewart Teppar strangely here has done the landmark study that shows that about 94% of patients that come to see a doctor with headache have migraine or migranous headache. So it seems to be coming more and more important.

The Triptans, this is probably the best treatment we've ever had, were invented and released around 1989. Now we have seven of them. It is generally recognized that migraine drugs like Triptans are only effective in 50-70% of patients for any particular patient. Since there's considerable failures with these Triptans, it's very important, I think as a headache specialist, that we have multiple options of treatment. In this case, multiple Triptan choices.

There was a recent conference I attended in Seattle of headache specialists where the consensus view is that we would all like to have about four of them at least tried on any significant patient. There's a strange paradox among the Triptans, and that's something that- again, thank you Stewart, we used to call the Teppar Paradox, whereas if you use a very effective drug early, even a very expensive drug, it saves money in the end because you avoid 2nd and 3rd dosing and also disability and days off of your life. In Medicaid patients I think it's particularly important, patients who are disabled and trying to

become fit for employment and trying to get their life going again to have particularly effective drugs and reduce disability whenever we can. Will Rogers said, I've never met a man I didn't like, and I must say I've never met a Triptan I didn't like, although we use different ones for different situations. I'd like to say a good word about Eletriptan. I really could say a good word about all of them actually. Relpax, which I see is an effective drug, I use it on a daily basis, multiple times a day, would be classed as a poet medicine, often effective. And a lot of my patients when they say the other ones have failed and have been through 3 or 4 of them. I see no reason to doubt the conclusions that it's at least as fast or faster than any of the other Triptans. I see no more particular adverse events by the sum of the literature to this. And its drug interactions, which can be considerable are to drugs that I have never used in my life and have never seen in my office in 25 years of practice, mainly the age drugs and a lot of unusual fungal drugs. All obviously doctors have to be aware of this.

I have arrived at these conclusions by the process of clinical practice. 70,000 patients and advisors did not pay me to come here to say this. I think it's good to have all the options available for treatment.

Carol Cordy: Thanks very much. I wanted to know, Mark, did you want to comment on any of the statements that were made, particularly on Larry Martinez request? Are you there, Mark?

Mark Helfand: I am here, yes. Can you all hear me?

Carol Cordy: Yeah.

Mark Helfand: Sorry. I guess I have a few comments. I certainly agree that in order to fully evaluate our work the meta-analysis needs to be peer reviewed. Now, typically, because we publish our results in these reports, we have these reports peer reviewed. What I think we should do in this case is write a separate document for the meta-analysis so that we can complete those steps. The speaker mentioned the Ferrari meta-analysis and Lancet, and just to review, that meta-analysis concluded anyway that 80 mg of Eletriptan and 10 mg of Rizatriptan or 12.5 of Almotriptan provided the highest likelihood of consistent success over 3 headaches. That was their main conclusion. There was nothing in the report that suggests, just to be clear, any advantage for Eletriptan 40 over the usual dose of Sumatriptan or Rizatriptan or the others. So the dispute really focuses on Eletriptan 80 mg. In doing their report those folks at the Ferrari Group had a finding similar to ours in that what they found was that in studies of Eletriptan, or studies done by the makers of Eletriptan at the time, a placebo was significantly less effective than it was for some of the other placebo groups in other companies' trials. And Sumatriptan was less effective than it was in the trials done by other companies, especially for the 2-hour pain free response. We agree with the speaker from Pfizer in that we

have no idea if that's because of encapsulation. But it is the anomalous result that needs to be explained. It might be explained by different criteria for a pain free response. It could be explained by a selection of patients. We can't really say it's encapsulation. Where our result differs from what the speaker said is in the narrow area where he was saying that Eletriptan performs worse in studies with encapsulation than in others. Now if that's true, it contradicts the point that he was making that encapsulation has no effect on the effectiveness of these drugs. So I wasn't quite clear on that, but just to reiterate, what we found was that for some reason- probably not, who knows, whether it's another reason or the capsule itself, but for some reason Sumatriptan appeared to be less effective when compared to Eletriptan than when it's compared to other drugs. And that's something that Ferrari found too.

[end side one, tape one]
[begin side two, tape one]

Mark Hefland: And the speaker thought that we should be clearer about. Finally, I agree; we should be clearer about that and we'll try to report the meta-analysis in full terms the next time around.

Carol Cordy: Thank you. Dr. Elena Robinson?

Elena Robinson: Good Morning. I am a neurologist from Headache Clinic at Swedish and I represent myself and my patients. Obviously what happens in this room this morning will affect my practice and the way I treat my patients. And in my opinion one of the very important aspects of any medication and the path that medication goes through is clinical practice. It's what happens in doctor's office after all the trials are completed and results are published. While certainly one can never underestimate the importance of Imitrex in treatment of migraine headaches, it is not a golden standard of therapy because if it was I would have much less patients to take care of and probably wouldn't have a job. And having treatment options is very important for the patients. There are several medications that have been repeatedly mentioned here today; Rizatriptan, Frovatriptan, Imitrex, Eletriptan and the comments that were made is onset of action, which in case of Rizatriptan is very fast, duration, action and side effect profiles and mode of delivery. The fact that Eletriptan has very fast onset of action and long duration certainly makes it an excellent treatment choice. The Imitrex various mode of deliveries assumes that the patient will need a second dose or repeated treatment. And hopefully with a newer medication that would not be the case and would not be necessary. And published trial that compared Imitrex with Eletriptan showed that there is a much less necessity for the patient to have a repeated dose of abortive medication after treatment with Eletriptan comparing with Imitrex. And the reason I think it's important to give that option to the patients is that there is such a large number of people, millions of people, suffering from migraine.

And unfortunately, we're far from being very effective in treating them yet. Limiting options would only lead to perpetuating this problem. Thank you.

Carol Cordy: Thank you. I wanted to just make one quick comment, which seems to come up each time that the preferred drug list does not preclude you from prescribing other medication. That the preferred drug list is kind of a first choice, but if a physician is, or a provider is signed up as an endorsing practitioner that there is an option of signing 'dispense as written' and being able to prescribe any of the other Triptans or any of the medications that aren't on the preferred list. The next- Barbara Wheeler.

Barbara Wheeler: Good morning. My name is Barbara Wheeler and I am a health science associate with Merk, the makers of Rizatriptan. I wanted to thank you for the opportunity to come here and speak to you on behalf of Rizatriptan this morning. I am going to limit my comments to the 4 pivotal clinical trials that were done looking at the efficacy and safety of Rizatriptan versus placebo. When we look at the results of these trials compared to placebo, as you know most patients report that when they look at a treatment for migraine, when they're looking at the Triptans, one of the attributes that they really need is fast, rapid pain relief. And patients taking Riza in these studies- what was found was that patients taking Rizatriptan 10 mg have a 20% chance of improving from moderate to severe to mild or no pain in as early as 30 minutes. This number is unsurpassed if you look at the prescribing information for all the other oral Triptans. This number is unsurpassed at 30 minutes. 67-77% of patients taking the 10 mg Rizatriptan improved from moderate to severe to mild or no headache pain at the 2 hour post dose end point. And when we look at nausea, which is one of the most common migraine associated symptoms that patients get with migraines- many many patients get along with their migraines, what we found was that 65-66% of patients taking Rizatriptan 10 mg had elimination of nausea at 2 hours.

Some of the most common adverse events, just want to make a comment about those were [unclear] fatigue, dizziness, somnolence, and these did not increase in frequency when up to 3 doses were given in a 24-hour period. Rizatriptan is available in 2 formulations in both the 5 and 10 mg doses. The first is the oral tablet and then the second is an orally disintegrating tablet, or the MLT formulation. The nice thing about the MLT formulation is that it offers a convenient dosing option for patients. They can take it anywhere. They can just stick it on their tongue- the wafer on their tongue, it dissolves within seconds. It is swallowed with the saliva and absorbed in the gut. And also for those patients who have nausea, which as I stated early many patients do, they don't necessary want to take additional liquid along with their medication. And the orally disintegrating formulation offers them a nice option in this area.

Lastly, Rizatriptan is a rapid and safe, effective and efficacious Triptan for the treatment of acute migraine and I appreciate your consideration of Rizatriptan for Washington state. Thank you so much.

Carol Cordy: Thank you. Dr. Anne Speiser.

Anne Speiser: Good morning. I'm Anne Speiser with Scientific Affairs at Ortho McNeil. Thank you for the opportunity today to add a little clinical information regarding Axert and its role in the treatment of migraine both with and without aura. Because our high quality head-to-head studies are still in the works it is important to pay attention to those other studies; the Ferrari meta-analysis and the other placebo controlled trials as was indicated in the OHSU report.

When we're trying to choose a Triptan, and as we've heard from the physicians present today, one of the most important things is to consider what's valuable to the patient and what's valuable to the physician. Towards this end, we have that which we can gain from listening to people. We also have some actually published studies looking at exactly this question. For instance Lipton surveyed patients and Dotex surveyed physicians, and there was strong concordance in these results that sustained pain freedom, consistency of response and tolerability were the highest priorities for both patients and physicians. Interestingly, in the Lipton study they also discovered that patients greatly prefer either a capsule or a tablet formulation for their Triptan administration. Now in these three categories the same pain freedom, consistency and tolerability Axert does and Almotriptan does rank very highly and we can see that in the Ferrari meta-analysis. And it's interesting to think about the differences between the Ferrari meta-analysis and the report from OHSU. And there are very clear differences; the report from OHSU has strived for a very strong scientific rigor, looking very specifically at the types of studies that were used and picking them for very very strong design. Now while this is very good for internal validity and certainly has it's place, it's of limited clinical utility because of its limitations and its ability to compare all the Triptans. As much as they tried to do that, the data isn't available. So we do need to turn to other studies such as the Ferrari meta-analysis. Because it casts a wider net, this analysis does provide this additional clinical guidance. And in the conclusions from the Ferrari meta-analysis Axert, or Almotriptan was indeed found to be one of only 2 FDA approved Triptans with the greatest likelihood of success as defined by sustained pain freedom and tolerability.

Now, if you will permit me a personal note, I am a migrainer, and Axert is my drug of choice and has been prior to its acquisition by Johnson & Johnson. I've tried other Triptans and Axert is the one that I can tolerate and it works for me every time and allows me a significant improvement in my quality of

life. I know if I have that pill with me when I get a headache, I can be fine in about 1 hour. Thank you very much.

Committee Deliberation and Vote

Carol Cordy: Thank you. Mark or Kim, do you have any additional comments? Are they there? Oh. I guess they don't. Any other comments from the committee? So I think we move on to- is there a motion? What I'd like to do with my wordsmithing here is- it looks like in the form here, since the studies were all efficacy studies, we ought to change effective to efficacious?

Jeff Graham: Carol, we have the motion that you made last year in March on the green sheet, right here. And you did use efficacious there.

Carol Cordy: Okay. Should I just repeat this? Or does somebody want to?

Bob Bray: I would suggest we read the motion and discuss if we want to change that.

Vyn Reese: The motion I made last year- that Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan [unclear] efficacious for the treatment of migraine. [unclear]. So it would be, 'After considering the evidence of state, efficacy of [unclear] treatment of migraines, I move that Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan are safe and effective…

Carol Cordy: Efficacious.

Vyn Reese: Yeah. Safe and efficacious. And is associated with fewer adverse events and special populations. Triptans can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of migraine.'

Unidentified: You move that.

Vyn Reese: I move that. That's my motion. I don't see any new evidence that's swayed me that there's any major difference in the [unclear].

Patti Varley: Patti Varley. I'll second that motion.

Carol Cordy: All in favor?

Many: Aye.

Carol Cordy: Opposed? The motion passes.

Official Motion

After considering the evidence of safety, efficacy and special populations for the treatment of **MIGRAINE**, I move that **ALMOTRIPTAN, ELETRIPTAN, FROVATRIPTAN, NARATRIPTAN, RIZATRIPTAN, SUMATRIPTAN, ZOLMITRIPTAN** are safe and efficacious. No single **TRIPTAN** is associated with fewer adverse events in special populations. **THE ABOVE NAMED TRIPTANS** can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of **MIGRAINE**.

Jeff Graham: Have you got it Donna?

Donna Marshall: Did you say you struck this exception?

Vyn Reese: Yeah. And just put Triptans there. Okay.

Carol Cordy: Break 'til 10:30?

Unidentified: Yep.

Carol Cordy: Okay. We'll take a break 'til 10:30. Thank you all for coming.

[break]

INTRODUCTIONS

Carol Cordy: And will give the presentation on the inhaled corticosteroids and then we'll have stakeholders come and...

Jeff Graham: Just a moment. Why don't we have- introduce ourselves [unclear] so, go ahead, Carol.

Carol Cordy: I'm Carol Cordy. Are we going to go around?

Jeff Graham: Well, then why don't you- and your specialty, Carol.

Carol Cordy: Oh, I'm a family physician in Seattle.

Angelo Ballasiotes: Angelo Ballasiotes, mental health in Yakima, Washington.

Vyn Reese: Vyn Reese, internal medicine and geriatrics in Seattle.

Janet Kelly: Janet Kelly, pharmacist.

Bob Bray: Bob Bray, family physician in Spokane.

Patti Varley: Patti Varley, child and adolescent psyche, Children's Hospital.

Jason Iltz: Jason Iltz, pharmacist member.

Jeff Graham: And then we have various staff from our three different agencies here. And so your slides are up there and ready to go.

INHALED CORTICOSTEROIDS
Update of Drug Class Review

Richard Hansen: Okay. I'll give you my introduction, then, in case that hasn't been done. My name is Richard Hansen and I am a pharmacist, but I am also Ph.D. trained specifically in outcomes research and I have been working with the UNC evidence based practice center now for almost two years doing these comparative drug class reviews. So I'll get started then. I've got an echo. Is there an echo there on your end?

Jeff Graham: No. I was just going to say, for us in the West UNC means?

Richard Hansen: University of North Carolina. Sorry. Actually, our evidence based practice center is joint with RTI, which is Research Triangle Institute. Okay. So I'll get started. This particular review looked at five different inhaled corticosteroid products. And we conducted the initial review beginning in April of 2004 so it includes all of those products that were available at that time in our initial search. We didn't include any combination products, but we did evaluate all possible product formulations for each of these products including meter dose inhalers, dry powder inhalers or nebula therapy. And each dosage form was characterized by respective delivery device. For instance, as we reviewed each comparative trial or a placebo controlled trial we made sure to know and make comparisons only among similar devices. And because some of the included studies were conducted outside of the US where alternative delivery devices were available, we noted that and tried to be consistent about any comparisons that we made.

Can everyone hear me all right?

Carol Cordy: Yes.

Richard Hansen: Okay. I'm on slide three right now of the presentation. And we evaluated evidence for the five different products in adult and pediatric outpatient populations with asthma, as well as adult outpatients with COPD. Slide four. We made an attempt to differentiate between efficacy studies and effectiveness studies. And the way that we did this was we considered effectiveness studies to be those that are conducted in primary care studies with few inclusion exclusion criteria- and this is quite a subject of determination. Basically we felt that the randomized population was

representative of a more general population. We considered that to be few inclusion exclusion criteria. We also defined effectiveness to be follow up greater than 1 year and it had to specifically look at health outcomes rather than intermediate outcomes. The specific health outcomes that we included were alleviation of symptoms, quality of life, ability to participate in work, school, or physical activity, which I'll refer to as functional capacity. We looked at emergency department or urgent care visit, hospitalization and mortality. And then for COPD we also included intermediate outcome such as lung function tests just simply because there wasn't a lot of evidence available for health outcome.

I'm on slide five. For tolerability and safety we evaluated overall adverse effect reports, withdrawals because of adverse effects, serious adverse event reports, and then we looked at a list of specific events including osteoporosis, growth retardation, acute adrenal crisis, cataracts and ocular hypertension and open-angle glaucoma.

Slide six. Study designs included in the review for efficacy and effectiveness were head-to-head trials, meta-analyses and placebo controlled trials, specifically if the placebo controlled trials included measures of quality of life, functional capacity or hospitalization. And the reason that we did this upon our initial scan of the literature we realized that we weren't going to be able to have a whole lot to say looking at these head-to-head trials of these comparisons. And also because the FDA wasn't requiring these measures for approval. We thought those placebo controlled trials were especially useful in this case. For safety and tolerability we included all the designs included for efficacy and effectiveness, but we also included observational studies. And for subgroups observational studies were also included.

I'm on slide seven. When we first started the review we were concerned about differences and potencies among different devices or different products. And we wanted to be able to assess dose equivalency. So we attempted to characterize equivalent doses using the National Asthma Education and Prevention Program, or the NAEPP expert panel report as it's listed in our full report. These are consensus guidelines for dosing and don't reflect evidence based medicine. But they were essentially all we had to go on to help guide our comparison. So we used these throughout our report and make reference to dose equivalents based on these guidelines. Where essentially we characterize the doses compared as high, medium or low consistent with the guideline. One important consideration with looking at comparable doses with these products is that the differences are in potency and not in the number of actuations required to deliver a comparable dose. So, for instance, 20 puffs per day of Triamcinolone would be required to deliver a comparable 2-3 puffs per day of Fluticasone and our report does not address that. We simply wanted to address whether or not we were looking at apples and apples; in other words, one dose compared to another similar dose.

I'm on slide eight. Our review for efficacy and effectiveness for asthma identified 19 head-to-head trials, 1 meta-analysis and 10 placebo controlled trials that included quality of life for measures of functional capacity. And no specific trial was characterized as an effectiveness trial so all of the trials that I am going to talk about were defined as efficacy trials or conducted in more narrowly defined populations.

Slide nine. For comparative efficacy the body of evidence is mixed. And for most included outcome measures, evidence supports no difference in the compared agents. But we did find that in 63% of trials or 12 of 19 trials there were significant differences and at least 1 outcome measure and that wasn't necessarily the primary outcome measure for which the study was powered, but simply that we did observe in one of the outcome measures there was a difference. And in most cases, when there was a difference, it favored Fluticasone over the comparator product.

Slide ten. This table represents results for asthma looking specifically at rescue medication use or Beta-agonist use. And I apologize for the abbreviations, but it's difficult to summarize all this information in one table. So for the purposes of this table, BDP reflects Beclomethasone, BUD reflects Budesonide, FLUP is Fluticasone, FLUN is Flunisolide and TRIA is Triamcinolone. So these are the- the number of trials listed that's the number of comparative trials for each of those classifications that we identified. And the evidence suggests that in 6 of the 19 trials there were significant differences reported for Beta-agonist use. In 2 of the 7 trials comparing Beclomethasone with Fluticasone, Fluticasone-treated patients used less rescue medication, and then 2 of the 5 trials comparing Budesonide with Fluticasone, Fluticasone-treated patients used less rescue medication. It is important to note here, though, in one of the two trials comparing Budesonide with Fluticasone, the compared dose of Fluticasone was higher again using the NAEPP guideline. The dose was higher than it was for Budesonide. Both of the Fluticasone versus Triamcinolone studies that we identified did use higher doses of Fluticasone as well, although they did find significantly less Beta-agonist use in those two trials.

I'm on slide 11. For asthma symptoms the trials used a variety of different scales to assess symptoms. So making comparisons across the trials is very difficult. I'll just give you an example. Some trials used the four-point asthma symptom scale, some used the seven-point asthma symptom scale. So, in other words, looking at the difference between one point on the four-point scale versus one point on the seven-point scale makes it difficult to draw the same conclusion. Some of the trials simply reported the number of symptom free days and didn't report how that was assessed. Only two of the studies reported significant differences in asthma symptoms between the drugs that they compared. So for one of seven trials comparing Beclomethasone with

Fluticasone fewer symptoms were reported among Fluticasone patients. And in one of the two trials comparing Beclomethasone with Triamcinolone Beclomethasone-treated patients had fewer asthma symptoms, but again in this trial the dose of Beclomethasone was greater than the dose of Triamcinolone, using the dosing guidelines.

I'm on slide 12. We identified one good rated meta-analysis that pooled comparisons of Beclomethasone versus Fluticasone trials with Budesonide versus Fluticasone trials. So, in other words, what they did is they had the pooled effect of Beclomethasone and Budesonide and compared that to the combined effect of Fluticasone and analyzed it this way. They found in this pooled analysis that there were no differences in asthma symptoms, exacerbation or Beta-agonist use between the pooled Beclomethasone and Budesonide compared to Fluticasone.

Slide 13. This slide reflects quality of life or functional status and gives you an idea of the limited number of comparative trials that included these measures. There were four head-to-head trials that reported quality of life or functional status. One trial compared Fluticasone to Beclomethasone and found no differences in asthma related quality of life. And the doses there were equivalent. Two trials compared Fluticasone to Budesonide. In one of those trials where there were equivalent doses, Fluticasone-treated patients had fewer days absent from work. In the second trial there were no differences in missed school, but Fluticasone patients had fewer disruptions in physical activity. And that trial, though, again, the Fluticasone dose was greater than the Budesonide dose. Then finally, one trial compared Fluticasone with Triamcinolone and found greater improvement in asthma, the AQLQ and, this is for Fluticasone-treated patients, but again a more potent dose of Fluticasone was given.

Slide 14. We identified 10 placebo controlled trials that specifically included measures of quality of life for functional status. These trials compared Beclomethasone, Budesonide and Fluticasone to placebo and found no differences- I'm sorry, and found that these drugs were significantly better on the quality of life and functional capacity measures that they used. We didn't identify any Triamcinolone or Flunisolide study to report quality of life or functional capacity.

Slide 15. So overall, efficacy studies provide mixed evidence, and for the most part at equal potent doses and administered through comparable delivery devices, we concluded that there were no differences. However, there were specific differences that need to be acknowledged. Overall, the grade of the evidence was 'fair' for asthma.

Moving on to slide 16, looking at COPD. Just to point out, currently there's no single non-combination product, inhaled corticosteroid product approved

by the FDA for use in COPD. And we didn't identify any comparative evidence conducted in adult population with COPD. We did identify 9 placebo controlled trials and 3 meta-analyses that provide general evidence of efficacy of [unclear] of the class or individual products.

For mortality on slide 17, there's fair to good evidence that the inhaled corticosteroid products do not reduce overall mortality, but there's no conclusive evidence for specific products.

Slide 18. The majority of trials that were reviewed did not detect significant differences in quality of life between inhaled corticosteroid treated patients and placebo treated patients. However, we did find one study that reported significantly slower decline in quality of life for patients treated- for patients with severe COPD who were treated with high doses of Fluticasone.

Slide 19. Evidence on exacerbations is mixed. We found one good meta-analysis that reported approximately a 30% reduction in exacerbation. However, in a smaller fair rated meta-analysis this conclusion was not reported and counters the larger, good rated meta-analysis.

Slide 20. We included a few PD studies looking at an intermediate outcome including FEV 1. There's fair evidence from 1 large meta analysis that inhaled corticosteroid treatment leads to a modestly slower decline in lung function.

In summary, for COPD, slide 21. There's no comparative evidence, and we felt that the overall grade of the evidence is 'poor' and that it's insufficient to draw any firm conclusions about comparative effectiveness.

Slide 22. Tolerability and Discontinuation Rates. Looking specifically at comparative evidence we did not find any significant differences in adverse events or discontinuation rates due to adverse events. Sorry. The overall rate of local side effects was less than 10% and most commonly included things like oral candidias, rhinitis, cough, hoarseness, bronchitis and sore throat. We did find a higher rate of upper respiratory tract infections and in some studies the range among different studies was 3-32%. And it seemed to be typically studies conducted in children or adolescents that had a higher rate of respiratory tract infection.

Slide 23. For specific adverse events the evidence is mixed. And looking at significant differences that were reported in the comparative trial, two trials reported a higher instance of sore throat for Fluticasone patients compared to Beclomethasone treated patients. One trial reported a higher incidence of oral candidias for Fluticasone treated patients compared to Triamcinolone. And one trial reported more upper respiratory tract infections for Triamcinolone compared to Beclomethasone.

Slide 24. This slide reflects our search for bone density and subsequent risk of fractures associated with decrease in bone density. And again, here the evidence was mixed. 3 of 7 studies, or 43% of the studies that we identified suggest that there's an increased risk of fractures and/or reduction in bone density associated with inhaled corticosteroid treatment, and this was especially true at higher doses. However, the evidence is insufficient to draw conclusions about one particular inhaled corticosteroid compared to another, and we felt that overall the grade of the evidence here was fair to poor.

Slide 25. For specific adverse events such as growth retardation we found two head-to-head trials looking- this is very important here, at short term growth. In other words, less than one year, where they found significantly less growth reduction under Fluticasone compared to Beclomethasone or Budesonide.

Slide 26. Looking at the rest of the evidence, however, specifically long-term growth, in one observational study looking at 9.2 years, there was no difference in adult height for Budesonide compared to placebo. And in most placebo controlled trials, there was significant reduction growth over a 1-4 year period compared to placebo. The reason that I point out the short versus long is that these are the studies that we included. There were some other studies that were excluded from our review for quality reason and we really struggled with this particular issue. Short-term growth there does appear to be significant reduction, but whether or not that translates into long-term growth we felt the evidence was very poor here and really only had one study looking at Budesonide to go on.

Slide 27. Looking at acute adrenal crises there was no evidence from controlled trials or observational studies. We did identify one fair meta-analysis of placebo controlled studies that revealed significantly greater dose related adrenal suppression for Fluticasone compared to Budesonide and Triamcinolone. But we deem this to be an intermediate marker for acute adrenal crisis and felt that the results really couldn't be extrapolated.

Looking specifically at cataracts, no study compared the risk of developing cataracts between one corticosteroid and another. In general the evidence of an association between an inhaled corticosteroid use and development of cataracts is mixed. If there is an association- or for those that did identify an association, it appeared to be related to higher doses, longer duration of treatment and older age, which could reflect the increased likelihood of developing cataracts on its own.

Looking at ocular hypertension and glaucoma, no study compared the risk of ocular hypertension or glaucoma between one product and another. We did identify two observational studies that provide consistent evidence of a dose related increase in risk for the inhaled corticosteroid treated patient. In this

observational study it wasn't looking at a specific product, but at inhaled corticosteroid as a class. We looked at different subgroups including age, race, gender and pregnancy to figure out if there was any evidence that would support greater efficacy or differences in safety or tolerability between these subgroups, and we didn't identify any control trial that compared one product to another for these subgroups. We did have a number of studies that we thought provided some indirect evidence for these things. In particular, slide 31 for age, there's indirect evidence from some trials conducted in pediatric populations or older populations that suggest that inhaled corticosteroid don't differ in efficacy or tolerability for these populations. However, the evidence is really insufficient to draw any conclusions about 1 product compared to the other, and indirect evidence in this case is really difficult to determine how adequate it is. For race, gender and comorbidities we didn't find any head-to-head trials that assess the impact of these subgroups with one drug compared to the other. And insufficient evidence exists to indicate any differences between these subpopulation characteristics.

We did a search looking specifically at pregnancy and found that no study evaluated the risk of pre-term delivery, congenital malformation, stillbirth or a reduction in birthweight or [unclear] for one inhaled corticosteroid compared to another. We did find, though, two observational studies that consistently concluded that babies born to mothers treated with inhaled corticosteroid were not at increased risks for these events. And we rated the evidence here as 'fair to poor.'

So slide 34. In summary, evidence is inconsistent and from a narrowly defined asthmatic population we found only minor differences in outcomes of various inhaled corticosteroid. There is insufficient evidence to draw conclusions about the comparative effectiveness or efficacy of inhaled corticosteroid for COPD.

Slide 36. Fair evidence exists that the overall tolerability of the products we compared does not differ substantially. There is fair evidence that Budesonide and Beclomethasone lead to greater reduction of short-term growth than done Fluticasone. However, there was the one long-term study for growth that did suggest no difference for Budesonide. And there's fair to poor evidence, which is inconclusive, to quantify the risk of bone fractures, long-term growth retardation, acute adrenal crisis, cataracts, open angle glaucoma or adverse perinatal outcome.

I'm on slide 37. I just wanted to go back to the point I made at the beginning regarding our dose equivalence. Again, this reflects only expert panel report. It doesn't consider the number of puffs per day that could effect adherence to the products and subsequent outcome. So had there been true effectiveness trials, this is something that we would have been something that we would have been very interested in identifying. And furthermore, we didn't consider

any variation in inhaler technique, and since the different products and formulations come with each of their own unique delivery device, there may be issues that are specifically related to the devices that are used. For instance, there's some evidence that older populations don't- are not as capable of using the self-actuated devices as compared to younger populations. That's just one example of where that might come into play.

That's the end of what I have prepared. So I believe you were going to open this up for questions, then.

Carol Cordy: Yes. Thank you. Are there any questions or comments from the committee?

Vyn Reese: Hi, this is Dr. Reese. Couple of comments. One I think the last issues to be considered that you mentioned are really critical and special populations. The elderly of- as you just alluded to have a difficulty using some of the metered dose inhalers and breath activated devices are more effective or more easily administered in my experience with my patients. The other question is is the number of puffs per day, and that also has a very direct effect on compliance because, as you mentioned too, you had to compare the potencies of the agents, and it- clearly, if you're having to give 20 puffs per day to get equal potencies, the client is going to suffer. So, even though there's not any good data in those areas, they are very important areas that we need to look at when we're making decisions in this group of drugs, which are very heterogeneous. It's more of a statement than a question, I guess.

Richard Hansen: Okay. Thank you.

Jason Iltz: This is Jason Iltz with the P&T. Rick, is it correct that at this point in time Budesonide is the only one that's an indication in pediatric patients less than or equal to four years of age?

Richard Hansen: To my knowledge that is accurate. Let me pull something out here quick. Actually, if you have the report there in front of you…

Jason Iltz: That's what the report says. I'm just making sure there wasn't something that needed to be updated since that report has been out.

Richard Hansen: Not that I'm aware of. But there is one correction to that table that we've come across since then. Apparently Fluticasone has an indication greater than 12 years for their Flovent product. For their metered dose inhaler. And no specific product, other than the Pulmacort Respules, is indicated for children less than four.

Jason Iltz: And then my other question, Rick, was is there- in going through these re-…

[*end tape one]*

[Tape 2 of 2]

Jason Iltz: possible side effects of growth retardation and those sorts of things. The study's not set up like that.

Richard Hansen: To be honest. I personally don't think the studies are set up well enough to look at that, but- the other thing that I didn't touch in this is funding. And I think that sponsorship of the trials has a lot to do with how the studies are set up. And Budesonide is really the only one that specifically the trials were going after the younger population. So I don't know if I'm getting at the root of your question. It's really- the evidence doesn't seem to be receptive to the needs of younger children. It's more including children in studies designed to assess older populations, was my assessment. Does that answer your question?

Jason Iltz: Yes. Thanks, Rick. And then just one more thing. In terms of data regarding osteoporosis or bone density loss. What were the duration of those? Do you remember? I mean, were they short duration? Were they long duration? How much time passed to look at that data?

Richard Hansen: Let me check. I don't know off the top of my head, but I've got it at my fingertips. It varied. I would say if you wanted a specific number, most were greater than 2 years. On average I'd say 3 years, and some as long as 6. I think there was one 9 year study.

Jason Iltz: Thank you.

Carol Cordy: Carol Cordy. I have a question. It seems like one of the problems with these studies is the dosing equivalents. And how do you figure that out, since they're all different? I mean, how do you say that the Fluticasone is a higher dose?

Richard Hansen: Well, I think what- and there may be someone in the room that's better prepared to answer this than I, but I believe the guidelines looked at comparative potencies, I believe it's using a skin blanching technique. So essentially what they did is we looked at those guidelines and then there's some evidence that rates the potencies based on lung function tests. I'm not doing a very good job answering your question, but I can…

Carol Cordy: I think somebody here may have a comment on that. Are there charts available that show those?

Richard Hansen: Yeah. If you go to the NAEPP report we've referenced the- it's available online. If you go to that report you can actually request a hard copy of it. They'll explain how they arrived at those dose equivalencies. And we simply

adopted their range of doses. And it's consistent with our chart and our report and looked at how the study defined their dose and characterized it that way.

Carol Cordy: Okay. Thank you. Just a comment. It seems like on a clinical basis that that's quite confusing because it would tell us we need to have people use more inhaled steroids of different kinds to get to the equivalent doses of the [unclear]. Is that- I mean, I haven't heard people say that, but…

Richard Hansen: I think that's inherent in this whole concept. There is that- there may be differences in outcomes depending on if you have a high dose or a potent dose of one product compared to a lower dose of another.

Stakeholder Input

Carol Cordy: Okay. Thank you. Other questions or comments. So I'm going to open this up. There are three people that have signed up; stakeholders to give comments. And, again, if you can limit your comments to three minutes. First of all, Dr. Rai. Is Dr. Rai here? Okay. Teri Wilcox?

Teri Wilcox: Good morning. Good morning. I am a pharmacist and work as a scientist for Glaxo Smith Klein in the Research and Development Division. I just wanted to make a couple comments with regard to the use of Fluticasone for treatment of asthma and COPD. First of all I'd like to highlight a couple things that Dr. Hansen said this morning and that is where there were differences among the agents it appeared that there was some benefit to your [unclear] Fluticasone for the treatment of asthma as well as the safety related to growth for children when they're treated with the various agents. Additionally you all have spent some time talking about this puff for puff equivalent and how many puffs of 1 gram versus another. What's interesting about Flovent is because it's available in three dosage strengths. That if the patient does need to go to a higher dose, then the physician can chose to write the middle or higher dose of Flovent so that the patient has to remember to take is still two puffs versus having to accumulate greater and greater number of puffs in their treatment. What's interesting about that is that the [unclear] Collaborative published in January, in fact January of this year, a report looking at Fluticasone and the varying doses of Fluticasone through their collaboration. And what they reported was that for most patients that have mild to moderate asthma, in fact the lowest strength, probably provide as much effect as the higher doses. So that's two parts to that. One of which is you're including that risk/benefit ratio, because for most patients you can use that lower strength. And secondly, there may be some cost benefit to the system in using the lower strength.

I wanted to build on that with one approach to effectiveness therapy, which is looking at health plan database data. In 2001 there was an article published in Respiratory Medicine looking very specifically at a health plan at the various

inhaled corticosteroid. And what they found was that using their Flovent 44 prescription as their reference point, that there was a lower monthly asthma cost and a lower monthly health care cost total for patients where they were filling Flovent prescriptions versus the other enhanced corticosteroid.

So I'd like to summarize really three points. One is to emphasize what was in Dr. Hansen's report about the benefits associated with Fluticasone. Secondly that the value of having an agent in three strengths so that you can minimize that confusion around the puff conversion as you need to increase therapy. And thirdly, there is at least one paper providing some evidence that there may be a cost benefit to choosing Flovent as the option for the [unclear]. Thank you.

Carol Cordy: Thank you.

Teri Wilcox: And I guess, did you get your question answered with regard to the dosing tables?

Carol Cordy: We've actually found the table here.

Teri Wilcox: Okay. All right.

Carol Cordy: Thank you. Randy Legg?

Randy Legg: Can you hear me okay? I'm pretty tall so I'll lean down. I'm a pharmacist. I work for [unclear]. I [unclear] the [unclear] portion [unclear] division. I live in Spokane. What I wanted to do was highlight a few things about our products that have been published since our initial submission to the Oregon PC, last year, April, 2004. First of all, [unclear] healer has a category B safety pregnancy rating, which is the only inhaled steroid which does have that rating, as well as [unclear] does. And to answer your question, Jason, we are down to [unclear] months [unclear] indication.

Last year there was a public paper and the start paper. And the start paper looked at long-term safety as well as outcome for patients treated with Budesonide for mild persistent asthma. We looked at outcomes and the Pulmicort [unclear] other group had increased to 14.1 symptom free days. They had a drop in hospitalizations by 69%. A drop in the ER by 67%. A drop in offices by 36%. And then a drop in school days missed by 37%. And that's compared to patients who were on Albuterol and customer treatment [unclear]. They were maintained on 200-400 micrograms of Pulmicort [unclear] once a day.

And then also Dr. Weiss took a subset of patients 5-10 years of age and they had an increase in symptom free days of 16 days per year, decrease in hospitalization by [unclear] percent. Decrease in the ER by 34%. Decrease in

school days missed of 24% and a decrease in 34% of caregiver days associated with patients maintained on Pulmicort inhaler.

So Pulmicort [unclear] nebulized steroid down for age 12 months to 8 years of age. There were a few papers published on that one as well. In addition it has a once a day dosing for maintenance. And it also has a category safety B pregnancy rating as well.

Dr. Burger published a paper last year in Journal Pediatrics and they concluded a safety trial of a .5-1 mg inhaled steroids per day had no difference compared to placebo in [unclear] suppression.

And then finally, I wanted to mention on slide No. 13 of the presentation there was a typographical error. It listed a quality of life paper comparing Budesonide [unclear] in the white margin administering Budesonide, I think that should be times [unclear] in the [unclear].

Richard Hansen: You're correct. Thank you. I see where you're talking about. My apologies for that.

Committee Deliberation and Vote

Carol Cordy: Thank you. Are there any other comments you want to make? Do you have anything?

Richard Hansen: I was trying to follow the studies that were just listed, and I can't specifically comment on them without- the Star trial sounds familiar as one that we reviewed. But I can't recall the specific author. So, in other words, no. But if you'd like more information, I'm happy to pull those specific references if you'd like to see how we assess them in our report.

Carol Cordy: Okay. Thank you. Was there anything on this chart that you [unclear]?

Unidentified Male: [unclear].

Carol Cordy: Mm hm. So, on this chart when there's comparisons of the differences in inhaled corticosteroids, that was the chart that was used for this report, is that right?

Richard Hansen: You're talking about, I believe, it's table 3?

Unidentitified Male: Table 3.

Richard Hansen: Yeah, that was the chart that we used, and we had two individuals abstract data for this report. What was done is first we had a trained abstractor go through each study and abstract the classified doses and there was an eight-

page evidence table that they worked on where they abstracted all the data from the trials and then characterized if it was a comparable dose. And that's really what we were looking for is to see if- make sure that we weren't reporting results of 1 low dose versus a high dose where it wasn't simply that we were looking at one drug versus another. But we wanted to make sure that we were at least aware of dose discrepancies. We tried to do this in other reviews that we've done where, for instance, if you're looking at one SSRI compared to another you don't want to look at 10 mg of Prozac compared to 300 mg of Zoloft. So this was our attempt to make sure that trials weren't purposely designed to favor one drug over another. So what- sorry, I go off on a tangent. But what we did is the first abstractor characterized that then and a second abstractor went through and reviewed all of the data and the tables and verified the equivalency. So you'll notice then here there's some overlap. For instance, Beclomethasone on the first line for an adult that range goes up to 504 micrograms. The range for a medium dose is 504 as well. We actually- this is the exact replication of the table provided by the NAEPP report. You can't classify it. If there was a 504 microgram dose there's overlap there. So in those cases we actually said that 505 and above was medium dose. However, one of the peer reviewers that we had when this report went out for peer review made a very big deal about this, so we decided to simply reproduce this. But just so you know, we did actually say if it was 505 or above for Beclomethasone CFC that was medium. Does that make sense?

Patti Varley: This is Patti Varley. Just point of clarification, the same chart that we were talking about, there was a typographical error of general efficacy for asthma with slide 13. So am I clear in saying that when you look at the results in the last 2 in the dosing equivalences, it's using this chart saying that the dosages were different when they were compared?

Richard Hansen: Correct.

Patti Varley: Okay.

Richard Hansen: For instance, in the last chart where there was- the error was Budesonide, it says Fluticasone dose greater than Triamcinolone, that would be suggesting that for instance we classify Fluticasone as a medium dose and Budesonide- I'm sorry, Triamcinolone as a low dose.

Patti Varley: Okay. Thank you.

Carol Cordy: Other comme- Carol Cordy. I think as we move towards trying to decide what to do with this, it's going to be difficult when we say use the subject for therapeutic interchange because you'd have to have this big chart to really say that these were interchangeable.

Jeff Graham: And Rick you're not aware that we have something different in our state, the only state in the 50 where a pharmacist can't interchange a drug within a therapeutic class that doesn't- it used to be that you could use a generic, but now we have it that the pharmacist could do that. And for some classes it's easier than others.

Richard Hansen: Okay.

Vyn Reese: What I'm really concer- this is Dr. Reese. What I'm really concerned about is the type of device, too, because they could substitute somebody who was using a metered dose inhaler, they could take a patient and put them on a metered dose inhaler when they were using a breath activated device and that may really adversely affect compliance. And that's another real concern I have with the therapeutic interchange law here. Also, it looks like just looking- just trying to organize our discussion, looking at all these different drugs, clearly we have to have something for pediatrics, the younger children. Clearly I think we have to have something that's breath activated for the elderly and we have to really give careful thought to potency and the number of puffs per day to get to a certain equivalent dose. I think those are the ways you have to organize the discussion, just off the top of my head, just looking at the chart and listening to this presentation. So it's- as I say it's a very heterogeneous group and it's not easy to compare some of the drugs given their differences in potency. And so it's going to be a difficult decision making process to sort of talar this to the patients and make sure that all of the sub populations of patients are actively- are effectively treated.

Carol Cordy: More comments. I think this is going to be difficult to know where to go and how to make this fit in with our [unclear] sub populations to deal with.

Richard Hansen: And again, I agree with you that all those are important considerations and I think maybe we need to approach it kind of like we did with SSRIs the last time and say, you know, first out task is to consider are these safe, are they efficacious, and then we move forward with are they subject to therapeutic interchange, yes or no. And then make the recommendation to say, You know, in considering that they appear to be safe and efficacious, we would like to see, you know, a representative agent that covers a pediatric formulation that, you know, addresses some of the other concerns in terms of the- a drip activated device, a metered dose inhaler. And then I think that giving them that direction, they would be able then to, you know, take the other information they have into consideration and put the appropriate things on the Washington PDL at that point. Does that sound reasonable?

Vyn Reese: Yeah, that sounds like a great way to do it.

Jeff Graham: Carol, I think if we have no further questions for Rick, we could probably let him go. Rick?

Richard Hansen: I'm happy to answer questions, if you have some, otherwise send me an email if something else comes up that I can help you with.

Carol Cordy: Okay. Are there any other questions? Okay. Thank you, Rick.

Richard Hansen: All right. Thank you. Good luck with this.

Carol Cordy: So, is anybody ready to attempt to say something on this, or should we discuss more? It does seem like we need to separate, as you say, the therapeutic interchange cases that's going to- it may be something we can't really include.

Jeff Graham: Well, well- this is Jeff Graham. And you have done some of that before two different ways. For the SSRIs you said they're not therapeutic in that they're not interchangeable. We've done some work in the past like on the long acting opioids and we got some help on giving directions to pharmacists how they might do that. And I think the Washington State Pharmacy Association has done some work on other drug classes on difference in potency and what would be the appropriate interchange there. And they've actually put that on their website for most of the other classes [unclear]. So I mean there are some ways we can look at it that have been done [unclear].

Vyn Reese: I, you know, I think we can sort of go through this and I think all the different exceptions are going to need to be listed as we make the motion because there are going to be [unclear] certain things for others and the drugs are really very similar, the delivery systems and the indications are different for some. So it's- we're really going to have to make a lengthy motion, I think, to cover all the necessary variances in the drugs.

Duane Thurman: Excuse me.

Vyn Reese: Does anybody else want to start?

Duane Thurman: Could I just give some background here? Duane Thurman from the Health Care Authority. I think that one thing that the legislature assumed going into this is that the pharmacist would play a part in the therapeutic interchange. And, you know, I just tell you in terms of having to make the assumption that they are knowledgeable within the skills of their profession to make certain decisions with regard to the devices, what's appropriate for the patient and- you know, I'm not saying you have a role one way or the other, but the legislation does assume a lot of responsibility on the pharmacist's part in terms of the therapeutic interchange. And, you know, you could consider that in terms of how you do it; whether you trust 'em or don't trust 'em. I think there's just an implicit assumption in the legislation that the pharmacists will play a pretty active role, they will have the conversion charts in front of them.

They are aware of the differences in terms of the devices and so I just give you that as background.

Vyn Reese: Yeah. I worry, Duane, though that they don't- they may not be sensitive to special populations and the devices and how important compliance is with certain types of devices and certain age groups. And so if you're not sensitive to that and it's not brought up to you in a in a really- up front as a primary consideration, you can cause somebody to have an asthmatic exacerbation, ER visit, it's not going to be good for anyone. So I think that we need to be really cautious how we craft this proposal to be sure we have drugs in the formulary that will meet special populations' needs.

Duane Thurman: No, I don't disagree at all. I'm just saying you've got the the discretion to do what you need to do. I just felt compelled to, you know, let you know what the discussions were during the creation of the legislation so that when I hear from other groups I can say that we did consider all these things.

Bob Bray: This is Bob Bray. I hear what you're saying, too, Duane. And I think that even with conversion tables, parenthetically, my wife's a pharmacist and I don't want to have her to have to deal with the exasperation of the patient when she tells them that according to the table, based on what we could do if we made it therapeutically interchangeable, that the patient's going to have to take 20 puffs a day of the medication. I think that's what we're all saying is that I'm concerned that that's not going to be doable from the patient's standpoint. I'm concerned that it's not going to be any kind of a cost savings to have to use low potency- that kind of volume of low potent drugs. So even though I think certainly the pharmacist can do that, I'm not sure that that's beneficial to do that. And so I guess with all this discussion, I'm favoring the idea that because of the- both the complexity, the difficulty and the fact that we have no evidence that we can make those conversions and effect the same outcome in the patient, that I would favor no interchange.

Carol Cordy: Carol Cordy again. I- early on in this process it was I think unclear to the committee what the State Pharmacy Association was doing, and I think we still haven't had that kind of information.

Duane Thurman: I don't mean to overstate the case. I just wanted to state that, you know, that that we're all in this together and the different parts are expected to work as well as possible. It's not like the legislature specifically thought about all of these issues. And I don't want to say that you don't have the discretion to look in terms of what is, you know, in your professional opinions subject to interchange. That's that's…

Carol Cordy: But is there a way that we might know what the Pharmacy's side of this is doing?

Duane Thurman: I mean, they do have information. They've tried to support in terms of general conversion guidelines and things that are on the Washington State Pharmacy Association's website, that sort of thing. I don't think there's necessarily a consensus on every- you know what I mean? A lot of these issues that come up if you review a new class of drugs aren't issues that anyone thought about when they passed this legislation. And so I'm just acknowledging that you have a difficult issue and, I guess, just putting in this idea that that somehow the legislature has plugged the pharmacists into this situation in a way that differs from the situation that we had before this, I think.

Carol Cordy: Oh.

Duane Thurman: So I don't mean to overstate it. And I don't think that there's any particular pharmacy lobby that's going to come and say, Well, they were not respecting our role in this. I think it's just a point of recognition as you go forward.

Carol Cordy: Well, and I guess, just specifically, for some of the other drug classes we've looked at, when a pharmacist gets a prescription- I'm just curious as to how then they decide- because we have a pharmacy in our clinic, too, how they decide which they're going to substitute- or, sorry, interchange.

Donna Marshall: When we went and did the training, one of the things would be first you would talk to your patient and find out what they've taken in the past, that they'd tried and failed or whatever before- you would- you'd counsel the patient. I mean, it requires that the pharmacist actually talk to the patient before he can change the drug. Unfortunately, there is no magic table for all these drug classes that tells me drug A at dose X = drug B at dose Y. It's based on a lot of the clinical professionalism of the pharmacist, their clinical knowledge of the different drugs and how they work, the side effects and the drug interactions. It requires them actually going through the profile of the patient to see what other medications that they're on. If they've tried and failed something, then I would assume that a pharmacist would not try to put them back onto that medication that they've already failed and at that point they would contact the doctor if there was nothing else to choose from. So I think in these cases- you have to remember with the interchange- the- making them non-interchangeable goes both ways. If I get a prescription at my pharmacy that says for somebody to take AsthmaCort 20 puffs 3x/day, I can't then give them, you know, Why don't we try Flovent at 2 puffs 3x/day. You know, so it goes both ways.

So when you're remembering about the interchange, if we make them not interchangeable, that also prevents the pharmacist from maybe improving care for the patients as well as, you know- I can't imagine that anybody would go from a 2 puff a day regimen to a 20 puff a day regimen, it would be the other way around. But, I think we- the legislature, WSMA supported this

legislation that you need to give the pharmacists the respect of the education that they've received and the care that they provide to their patients and allow them to make some of these decisions in combination with the provider that's actually prescribing them. Knowing- being a pharmacist myself, if I had any doubt about what to do, I would definitely pick up the phone and talk to the doctor to see if they had any better ideas. So I think it really needs to be left between the pharmacist and the prescribing physician to make some of those judgment calls.

Vyn Reese: I think I'm ready to try a motion, okay. I think that we…

Duane Thurman: Let me just- I don't want to start the debate between pharmacists and this and that. I didn't mean to do that.

Vyn Reese: No, no. I think that that's not appropriate. I think we need to make sure we craft this, we give the pharmacists room to do what's right, okay.

Duane Thurman: Well, I think that we [unclear]…

Vyn Reese: So we don't narrow their choices.

Duane Thurman: Right.

Vyn Reese: And we need to make a bro- give it a broad enough motion that we cover all the different possibilities so that the pharmacists have enough tools in their tool bag to be able to dispense the right drug. Okay.

Duane Thurman: Right.

Vyn Reese: And the physician's able to prescribe the right drug.

Duane Thurman: And I guess the point is we're staff. You have pharmacists on the committee. We leave it to you to make the decision.

Jason Iltz: Vyn, before you do that, I want to- and maybe this isn't the right question to this body, but I had a actually a call from a pharmacist about two weeks ago who was looking for those dosage conversion tables. And I thought they were on the WSPA site and I myself could not find them. Is it under a restricted to where it's for members only? Or is there a link to the Rx.wa.gov site?

Donna Marshall: I think they are members only, but if the pharmacist actually calls WSPA they will give them a password so that they can obtain them.

Jason Iltz: Okay. Because he was not able to get in. It seemed like a protected site. And so I guess that just brings maybe you know, there should be some work with WSPA to say, Boy, you know, everyone needs to have access to those, and

quick access that wouldn't require calling or something like that too. 'Cause I think it would help expedite, no matter what class we're talking about. That everyone in this state, all pharmacists, all physicians, everyone active in health care knows where those tables are at.

Duane Thurman: And you can refer those calls to Erika and we will set something up to try to make it as easy as possible and we will continue to work with the Pharmacy Association [unclear].

Vyn Reese: Okay. I'll go ahead and try, if that's okay. After considering the evidence of safety, efficacy and special populations for the treatment of asthma/COPD- we don't have as much evidence for COPD, parenthetically, I move that Beclomethasone dipropionate, Budesonide, Flunisolide, Fluticasone and Triamcinolone are safe and effective, period.

Carol Cordy: Efficacious.

Vyn Reese: Safe and…

Carol Cordy: These were not effective.

Vyn Reese: [unclear] all right. Efficacious. We'll get this right eventually. No single inhaled corticosteroid is associated with fewer adverse events in special populations. Devices- a pediatric product needs to be included in this list, comma, a high potency product in which can be administered in four puffs per day or less also needs to be included, and a breath activated device needs to be included in the list, period.

Carol Cordy: Great. [unclear].

Vyn Reese : So pediatric product, comma, high potency product, which can be administered in- I [unclear] the end out of half the products, yeah. Which can be administered in four puffs per day or less. And a breath activated device must be included on the Washington Preferred Drug List.

The next one is the hard part of it. These products can be subject to therapeutic interchange on the Washington Preferred Drug List for the treatment of asthma and COPD, provided the other- the above concerns are addressed. That way we can give the pharmacists enough room to stay within the guidelines and this should cover every- as far as I can see every possibility, but please have the committee help me out.

Carol Cordy: Okay.

Vyn Reese: This is tough.

Carol Cordy: I'm I'm just wondering if we need to state in there using [unclear] imperatives, whatever it's called. Tables. In the [unclear] you say it's going to be subject to therapeutic interchange using these tables.

Vyn Reese: Using the NAEPP dosing estimates. NAEPP comparative dosing…

Unidentified Female:Comparative dosing…

Vyn Reese: Comparative dosing estimates table.

Carol Cordy: This is Carol Cordy again. I'm wondering if we can with the one study that showed that there was a improvement in growth or less growth- fetal growth problems with Fluticasone, if we can really say there there's not one that's associated with fewer adverse events.

Jason Iltz: Yeah, I agree, Carol. I would strike the statement- this is Jason. I would strike the statement that talks about associated with fewer adverse events in the special populations. Just take that out would be my recommendation. Because I think we're addressing the differences in the next statement. And then in that following statement I would also include something, some statement regarding the use during pregnancy, in addition to the pediatric part of it. I don't know if we want to say specifically a class or just a- something that is safe for use during pregnancy.

Patti Varley: Well, the problem with that is that nothing is ever deemed safe during use in pregnancy so we have to be a little bit careful about that.

Vyn Reese: All the drugs look relatively safe, although one has a class B…

Patti Varley: Right.

Vyn Reese: Category B, so it may be safer, but we don't know.

Patti Varley: That's- so I was wondering, could you- this is Patti Varley, could you put it as category B, that you make sure that pregnant women have access to category B.

Jeff Thompson: This is Jeff Thompson. You know, as far as any kind of prior authorization, I mean, all they'd have to do is say, you know, if there's pregnancy needs and it would be authorized. I mean, this isn't about any type of restriction. So- I did have one question on the breath activated. So you don't believe a spacer is equally efficacious to a breath activated device?

Vyn Reese: Well, in some studies the spacers aren't as good. So I'm a little reticent to have that as being a therapy interchange.

Jeff Thompson: Just making sure it's clear.

Carol Cordy: Are there any other additions or changes to this?

Donna Marshall: I'm just trying to make it so we can read it a little bit easier on the screen.

Carol Cordy: And then we'll let Vyn read it again.

Donna Marshall: I also wanted you to know that I put COPD in there only because that was one of the indications addressed in the report. It's not necessarily one that I felt, you know, that you had to actually include in here. So that's still up to you guys to decide.

Jason Iltz: This is Jason again. So given Jeff's comment, I would be happy with taking the pregnancy statement out, knowing that something would be available to them, if that was a concern of the rest of the panel would agree with that.

Jeff Thompson: This is Jeff Thompson again. And that would be true with any drug…

Jason Iltz: True.

Jeff Thompson: that would- that had any type of rating for pregnancy.

Jason Iltz: And I think the less we tie the department head's hands the better here. And then do we need to specify dose when we say high potency? That's just a question. I mean, or do we leave it to say, Hey, we want something that's more of a high potency on there?

Vyn Reese: The problem is it's high potency if you give enough puffs of a weaker drug. It's like if you give 20 puffs of some other product it's going to be still high potency because that's the total number of puffs. That's not really true, but…

Jason Iltz: But most of the potency tables are based on, you know, high, medium and low potency. So that's where I was coming with the potency statement. But you're coming in more in terms of a total daily dose meaning potency?

Unidentified Male: This one [unclear].

Jason Iltz: Okay. Okay.

Vyn Reese: This this table here, the NAEPP, you know, table. Some- like for Beclomethasone see a high potency is 10 puffs a day. Over 10 puffs a day.

Jason Iltz: Right. So based on dose itself…

Vyn Reese: That's a lot of puffs. So, I mean, for some agents. So basically, you'd want an agent that's more potent than that that would require fewer puffs per day. That's my view.

Jason Iltz: And then is it okay to refer specifically to this table? I mean, is this the all-telling table? Or is WSPA going to have something different on there? I guess that's the other question I have is if we refer only to this table does that mean therapeutic interchange cannot happen unless someone has this specific table and only this specific table?

Donna Marshall: WSPA voluntarily- it was actually the residents at Harborview that developed the clinical PERLS that they have on their website. I'm not sure if those are going to be updated or what they actually used, but I'm assuming that they used the available published data that was out there. We cannot make WSPA take their information down. It's a voluntary tool that they've given to the pharmacists. It's also difficult, I think, to say that they absolutely have to go exactly by this table when there may be other recommend- I think we could recommend that they use this table and possibly put it on the web- our website so that it is readily available to those pharmacists, but I think it's- I would really think it's difficult for us to dictate to the practitioners out there that they have to use this tool as opposed to another one that might be their clinic tool that they've been told to use.

Jeff Graham: This is Jeff Graham. What we might say- this is just a thought. Can be subject to therapeutic interchange using comparative dosing tables such as the NAEPP in the Washington- such as, and then give that as an example.

Carol Cordy: Carol Cordy. Do we want to relook at the COPD issue and just leave that out? Or what do you want to do with that?

Vyn Reese: There's there's some data that's not very good.

Carol Cordy: Right.

Vyn Reese: But it does it does sort of prevent the [unclear] decline. And so it's very weak, and more research needs to be done in that area. I mean, there are providers that are doing it in those severe COPD patients as a trial, so it's one of those areas where there's not good evidence. So I'd hate to take it out and just say- 'cause some of these COPD patients have asthma, too, and that's the problem, and it's hard to- they had asthma as a child and then they smoked and they have both. And so it's hard to- sometimes it's not a clear cut thing to say, Well, just 'cause the guy's over 65 he doesn't have asthma. And that's what you could do and say, Well, you shouldn't give him an inhaled corticosteroid. It's hard- there's a lot of overlap between those two groups, too.

Janet Kelly: I'd like to speak to that to a certain degree. I think that in my practice what I've seen is that a lot of patients that have COPD and no asthma are receiving these drugs in lieu of drugs that really would be better served for them. So I would argue that we should take COPD out of it. And I don't think age alone says that if you're 65 you can't have asthma. We know that asthma is a life-long disease, so I don't think that is a big issue there, but I think from a teaching standpoint I see that these drugs are used inappropriately for COPD and I don't think that we should be supporting that by putting it up here. It's definitely not a first line therapy in COPD. I think we can all agree on that. And we're sort of talking about a preferred drug list that implies first line therapy to most.

Vyn Reese: You're right. There are other drugs that are better and it's like a last gap treatment when nothing else works, which- and so I agree and I don't think we should encourage that. Maybe we should just strike COPD. I think that's- because anybody- as long as you don't make it- put some age limit or something on it, too, because asthma doesn't stop at age- at old age- at older ages.

Patti Varley: This is Patti Varley. As a point of clarification to the point you guys are making and that is, is there ever a case when you don't have asthma and you have a COPD patient who is on other first line treatment that would have this treatment done in conjunction with as a complimentary treatment?

Janet Kelly: Sure. There's going to be cases where there's a patient who's on every other therapy and they add that and maybe it is appropriate, but as I'm saying we're talking about a preferred drug list. We're talking about first line therapy. That's not first line therapy. That's where I think that, you know, sign dispense as written and you're fine. But to me it's like that is not a big enough population to put you know, on our list.

Carol Cordy: Does anybody have a strong feeling not to strike it? Robert?

Bob Bray: This is Bob Bray. I guess my concern is I think everybody's right. And I hear your point, which is we shouldn't be doing anything that makes it sound like we support the use of this as therapy in COPD. The converse I guess I'm concerned about. I'd like to hear some reassurance that when someone uses it that our lack of an indicator on here is not going go wind up being a…

[end side one, tape two]
[begin side two, tape two]

Jeff Graham: Well, I think that's kind of the dilemma in how we do this anyways. We always search by indication and then we state by indication and I guess I just want to make sure that we don't wind up having a reverse limitation where people have to start justifying the use.

Duane Thurman: No, I think that, you know, again, we've stretched the limits of what we can do with a preferred drug list as opposed to what the individual treating physician would do in their expertise. And I think this is a situation where it's a lack of evidence, not evidence that it's one way or the other. And I think it's exactly what the dispense as written override was meant to do. And, Jeff, I can't see a way that we would end up using this to exclude treatments.

Jeff Thompson: And from [unclear] perspective, again, the dispense as written, so you get whatever you want if you're an endorsing provider. And then typically what we do with any of the prior authorizations, or even EPA, is tried and failed. If you can demonstrate tried and failed, you get what you need. And you get what you need for a year. And we can even post that. As a matter of fact, I mean, what we're trying to do is reduce the amount of prior authorization and go to EPA and cover the issues that you need to do is, you know, do you always get the Cadillac first or- when there's no difference between the Volkswagen and the Cadillac. I mean, that's what [unclear] here.

Duane Thurman: And could you clarify what you rely on in terms of EPA to meet that criteria?

Jeff Thompson: Under our WAC or our prior authorization we look at three components; we look at safety, we look at misuse/abuse, and we look at high cost and low cost alternatives. And I'd be more than happy to- we now have a matrix of- it's not just all of those, it's where you find evidence of safety that's good evidence, or evidence of misuse and abuse [unclear], and it's a high cost with lower cost alternatives, that's when we typically would PA [unclear]. And then when it's…

Duane Thurman: I guess I was just getting to EPA- If I come in…

Jeff Thompson: I'm getting there. With EPA we're sort of mediocre risk, that's when we do an expedited prior authorization. There's some evidence, maybe a little bit of safety, maybe a little bit of misuse/abuse, or there's- you know, it's medium costs but there are lower cost alternatives. That's when we get to an expedited prior authorization.

Duane Thurman: I guess the point is how has- how much of a hassle is it for the patient. I come in, I say I've got this condition, does that satisfy the EPA [unclear]?

Jeff Thompson: And so on an EPA, if the client were to say, Hey, I tried and failed the purple inhaler and I want the blue inhaler, that's good enough, the pharmacist enters in an EPA code and we take- because EPA has to happen at the point of service, not in interaction between the pharmacist and the doctor. So what we try and do is design EPA so that the pharmacist could ask a couple questions and if the client says that I found that the purple inhaler- I liked the yellow inhaler, good enough.

Duane Thurman: And I don't mean to suggest we're placing prior authorization or EPA on this particular class of drugs.

Jeff Thompson: But I'm just stating what the rules of prior authorization are. And we're really trying hard [unclear] to justify why we do prior authorization based on a risk analysis, not just looking at costs.

Jason Iltz: I think if you look- if we get back to discussing the evidence of what we have, I'm not sure we can include COPD in the very first statement of being safe and efficacious. Okay. We have limited efficacy data, certainly safe probably. But if we're going to address COPD we probably need to do it in a next sentence or a separate statement or leave it out of the statement itself. I mean, from that standpoint. So I mean, if you get really back to the evidence, it's not much there.

Carol Cordy: Do you want to go ahead and read it again without COPD on there?

Vyn Reese: It was taken out already and I agreed to that. I think that's a wise move. So this will be the final motion. After considering the evidence of safety, efficacy and special populations for the treatment of asthma, I move that Beclomethasone dipropionate (MDI), Budesonide (DPI, nebulization), Flunisolide (MDI), Fluticasone propionate (MDI, DPI) and Triamcinolone acetonide (MDI) are safe and efficacious. A pediatric product, a high potency product, which can be administered in 4 puffs per day or less, and a breath activated need to be included in the Washington State Preferred Drug List. For the treatment of asthma on the Washington State Preferred Drug List the inhaled corticosteroids can be subject to therapeutic interchange. Comparative dosing tables such as the NAEPP comparative dosing table- that's sort of redundant. Let's see. Using comparative dosing table- just leave out that second comparative dosing table.

Carol Cordy: [unclear] recommendations, guidelines?

Vyn Reese: Can be subject to therapeutic interchange using comparative dosing tables, such as the NAPP, as long as the above concerns are addressed.

Jason Iltz: You need to say [unclear].

Vyn Reese: What?

Carol Cordy: Might have to spell it out.

Jason Iltz: [unclear] whether it's a guideline or…

Jason Iltz: How about therapeutic interchange using resources such as the NAEPP dosing table?

Vyn Reese: Does anybody know what the NAEPP stands for? Do we have it written down?

Unidentified Male: It has to be written here somewhere. National Asthma Education Provider Panel.

Vyn Reese: Thank you.

Jason Iltz: And expert panel report.

Vyn Reese: Expert panel report.

Unidentified Female: It's Education and Prevention [unclear].

Unidentified Female: We'll make it up [unclear].

Donna Marshall: Program or panel?

Unidentified Female: Program.

Unidentified Male: Program.

Jason Iltz: And then abbreviate it.And then it's considered after that it's an expert panel report.

Carol Cordy: Do we need to say as long as the above considerations are addressed? Isn't that redundant? Or isn't it? 'Cause you've already…

Vyn Reese: Well, that would be- that would prevent the therapeutic interchange for different devices and different potencies and all the other things that we talked about up above, basically. Those are sort of caveats guiding the pharmacist on how to therapeutically interchange if that's necessary. It's just sort of moving it back up to the top. I mean, we could leave it out, if you think it's insulting. I need all the reminders I can get.

Carol Cordy: Are there any other comments or changes?

Donna Marshall: I just have a- I mean, if you don't like the way that it says taking the above concerns into- or as long as the above concerns are addressed, we could put taking into consideration the, you know, pediatric dosing or the dosing device above.

Vyn Reese: I don't want to repeat it all, though.

Many: Yeah.

Vyn Reese: I don't know. We could leave it out, or we could just leave it as it is, you.

Duane Thurman: I think, although it may not be pretty, it's clear. And…

Carol Cordy: Do we have a second?

Bob Bray: Second.

Carol Cordy: All in favor?

Many: Aye.

Carol Cordy: Opposed? The motion is passed.

Official Motion

After considering the evidence of safety, efficacy and special populations for the treatment of **ASTHMA,** I move that **Beclomethasone dipropionate (MDI), Budesonide (DPI, nebulization), Flunisolide (MDI), Fluticasone propionate (MDI, DPI), Triamcinolone acetonide (MDI)** are safe and efficacious. A pediatric product; a high potency product which can be administered in 4 puffs per day or less; and a breath activated device must be included on the Washington Preferred Drug List. **FOR THE TREATMENT OF ASTHMA ON THE WASHINGTON PREFERRED DRUG LIST, THE INHALED CORTICOSTEROIDS** can be subject to therapeutic interchange using resources such as the National Asthma Education and Prevention Program (NAEPP) expert panel report, **AS LONG AS THE ABOVE CONCERNS ARE ADDRESSED**.

1:30 meeting adjourned

WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

Regular Meeting

Radisson Hotel SeaTac

2:00pm – 4:00pm

Council Members Attending: Alvin Goo, Pharm D, Patti Varley, ARNP, Carol Cordy, MD, Robert Bray, MD, T. Vyn Reese, Angelo Ballasiotes, Pharm D., Jason Iltz, Pharm D., and Janet Kelly, Pharm D. John White, PA, was present by conference call.

Medical Assistance Administration, Coordinating Staff: Jeff Thompson, MD, MAA Chief Medical Officer; Joan Baumgartner, MD, Medical Consultant, MAA; and Nicole Nguyen, Pharm D, Clinical Staff Pharmacist, MAA

I. ADMINISTRATIVE ITEMS

The meeting was brought to order by acting Chairperson, Carol Cordy, MD. The minutes of the previous DUR Board Meeting in February, 2005 were approved.

II. Drug Class Review of Antiepileptic Drugs in Bipolar Disorder and Neuropathic Pain

A) Oregon Health Science University (OHSU) review

OHSU presented the review of antiepileptic drugs for bipolar disorder and neuropathic pain which was produced by Southern California Evidence-based Practice Center. Evidence which meet inclusion criteria was fair to poor in quality.

There was no evidence that any of the following were more effective than the others for the treatment bipolar disorder: carbamazepine, lamotrigine, phenytoin, topiramate, or valproate/divalproex. There was no evidence showing gabapentin was better than placebo for the treatment of bipolar disorder.

There is fair evidence for gabapentin which shows it is effective in the treatment of neuropathic pain. Overall evidence showing effectiveness in treating neuropathic pain was poor for carbamazepine, lamotrigine, valproate/divalproex, phenytoin, and topiramate.

No clear evidence of clinically significant differences in adverse events and withdrawals between the antiepileptic drugs.

B) Anti-epileptics used as Mood Stabilizers Stakeholders' Workgroup + OHSU Evidence-Based Report= MAA's DUR Board Proposal

Jeff Thompson, MD presented the attached proposal from MAA resulting from the mental health stakeholder meetings. This proposal provides Expedited Prior Authorization (EPA) codes for the pharmacy to input for the 4 antiepileptic drugs (gabapentin, Keppra, Topamax, and Gabitril) when they are being prescribed for their FDA approved indications. When used, these EPA codes will allow the prescription to be filled without prior authorization.

Comments from the DUR Board included recommendations to consider unintended consequences of stopping therapy and switching to other treatment options such as atypical antipsychotics, and to review evidence for off-label use and grade it. It was stated that this was a good project and providers need to look at why they are prescribing a drug and if there is no evidence, they shouldn't be doing it. It was also suggested to include the other antiepileptic drugs studied in the OHSU report in the education regarding off-label use. MAA will only include these four drugs at this time.

Dr Thompson will send out an email to the DUR Board members for the members to respond to and provide feedback on diagnosis'/ICD-9 codes to review for evidence for off-label use.

III. MANUFACTURERS' PRESENTATION

None

IV. STAKEHOLDERS' PRESENTATIONS

Joel Neier, President and CEO of Epilepsy Foundation Northwest. Mr. Meyer thanked the P & T committee on behalf of Epilepsy Foundation Northwest and the people with epilepsy in Washington and Oregon. He thanked the P & T committee for listening to their input and applauds the P & T committee's direction in ensuring that there are no impediments to prescriptions for seizure medications. He encouraged the committee to continue in this direction and provide people with epilepsy access to the right medication at the right time.

Mark Avery, psychiatrist in King County. Mr. Avery thanked the committee for their efforts. He is on the stakeholder committee. He applauded MAA's work on clarifying the use of these medications. During his work he spends more time discontinuing the use of Neurontin in patients rather than prescribing this medication. He does agree with the issue of a catch 22 situation since there are some off-label uses of these medications for certain psychiatric conditions, but hopefully they are not purely used for bipolar mania or bipolar depression but for other psychiatric symptoms/syndromes. He appreciates any help the P & T committee can add in addition to the stakeholder committee. He is comforted by the committees concern of using just pure evidence in the decision to use or not use these medications. In psychiatry they use expert consensus guidelines and community consensus, and the committee should look at these forms of data. To keep obstacles down as much as possible to appropriate

prescribing of these medications is important. With the antipsychotics, looking at the use of naturalistic style data as much as possible as opposed to controlled data would be helpful. There is one study that indicated that less than 7% of depression patients would qualify for a depression study due to co-existing medical, psychiatric and substance abuse disorders. Most of the evidence therefore does not apply to 93% of patients. This is where you get into the art of medicine, community standards, and expert consensus guidelines.

V. RECOMMENDATIONS OF COUNCIL

Council members will provide feedback to Dr Thompson regarding ICD-9 codes to review for evidence.

ADJOURNMENT